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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/773,773	02/05/2004	Timothy F. Kowalik	UMY-079	8486

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LAHIVE & COCKFIELD, LLP
ONE POST OFFICE SQUARE
BOSTON, MA 02109-2127

EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/773,773	KOWALIK, TIMOTHY F.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30,38-43 and 45-64* is/are pending in the application.

4a) Of the above claim(s) *8-26,46 and 51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,27-30,38-43,45,47-50 and 52-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11-30-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on and November 30, 2007.

Currently, claims 1-7, 38-43, 45, 47-50, and 52-64 are under examination on the merits.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 112, enablement

Claims 1-7, 38-43, 45, and 47 remain rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement for the reasons of record as set forth in the Office action mailed on May 30, 2007 and for the reasons stated below.

Applicant's arguments filed on November 30, 2007 have been fully considered but they are not persuasive. Applicant argues that the specification provides sufficient description to enable one of skill in the art to practice the invention at the time the application was filed. In so

doing, applicant merely contends, "Applicants have made an important discovery...regarding a class of molecules that have utility for inhibiting CMV." Applicant's attention is directed to the scope of the claimed invention. The instantly claimed invention is not directed to "a class of molecules that have utility for inhibiting CMV"; rather, it is directed methods comprising an RNAi agent targeted to CMV, wherein the methods embody *in vivo* therapeutic methods for treating various diseases. Applicant also argues that there are a number of research articles that support the enablement of the invention, all of which are post-filed references. Even the reference relied upon by applicant in arguing for the retinitis treatment method was published after the effective filing date of the instant application. The standard for determining whether or not the claimed invention in its entirety was fully enabled is to look at the state of the art and the skills of an ordinary artisan prior to or at the time the invention was made. The specification must be enabling as of the filing date. See MPEP §2164.05. The post-filing reference by Schmidt was cited to point out the siRNA delivery issue still remains as a major obstacle for many siRNA pharmaceutical industries and to emphasize that the claimed methods comprising administering siRNA molecules to any tissues/cells *in vivo* were highly unpredictable at the time of the invention. As evidenced by the applicant's selection of references, all of which are published after the application filing date, the state of the art and the level of skills commensurate in scope with the claimed invention were far from being well-developed as of the filing date.

Applicant further argues that the *in vitro* working examples that demonstrate reduction of IE1 and IE2 gene expression in human cells comply with the enablement requirement and that "A rigorous or an invariable exact correlation is not required".

First, applicant's attention is again directed to the breadth of the claimed invention, which embraces therapeutic methods that are claimed to treat diseases.

Second, the ability of an siRNA molecule to reduce IE1 and IE2 gene expression in cell culture does not reflect its ability to "target" the desired treatment area, thereby "treating" the claimed diseases.

Third, applicant is advised to review the cited *In re Brana* case, which is irrelevant in the instant case, as the decision made in *In re Brana* is a completely different case from the instant case. In *In re Brana*, the specification disclosed test results of several compounds within the scope of the claims, which exhibited significant antitumor activity against the L1210 standard tumor model *in vivo*. In the instant case, however, no pharmaceutical compound within the scope of the claims was disclosed, and moreover, no animal model was used. Applicant's argument citing *In re Brana* is therefore non-analogous and irrelevant to the claimed invention. (emphasis added)

Fourth, with regard to disclosing working examples, MPEP §2164 teaches that "Lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art." Note that "if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling."

See also *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) which teaches the following: "Nascent technology, however, must be enabled with a ***"specific and useful teaching"***. The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent

from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology." (original emphasis)

Since the amount of guidance or direction needed to enable the invention is ***inversely*** related to the amount of knowledge in the state of the art as well as the predictability in the art, and since RNAi technology directed to treating retinitis, pneumonitis, restenosis, cervical carcinoma, prostate cancer, adenocarcinoma of the colon, disseminated viremia, and organ dysfunction by administering a CMV-targeted siRNA molecule was underdeveloped and therefore considered as nascent technology as of the earliest filing date sought in the instant application, and since there is no enabling disclosure pertaining to any treatment whatsoever in a subject, it is reasonably concluded that, in view of the totality of the factors listed above and the evidence/arguments provided by applicant, the specification fails to comply with the enablement requirement, thereby necessitating undue experimentation for one of ordinary skill in the art to practice the claimed *in vivo* methods in mammals.

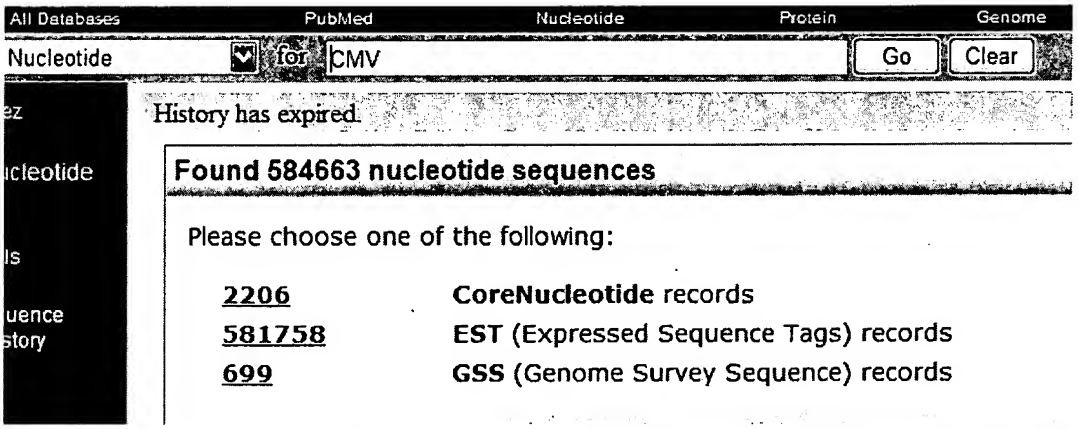
Also see *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991), wherein a rejection under 35 U.S.C. 112, first paragraph for lack of enablement was appropriate given the relatively incomplete understanding in the biotechnological field involved, and the lack of a reasonable correlation between the narrow disclosure in the specification and the broad scope of protection sought in the claims.

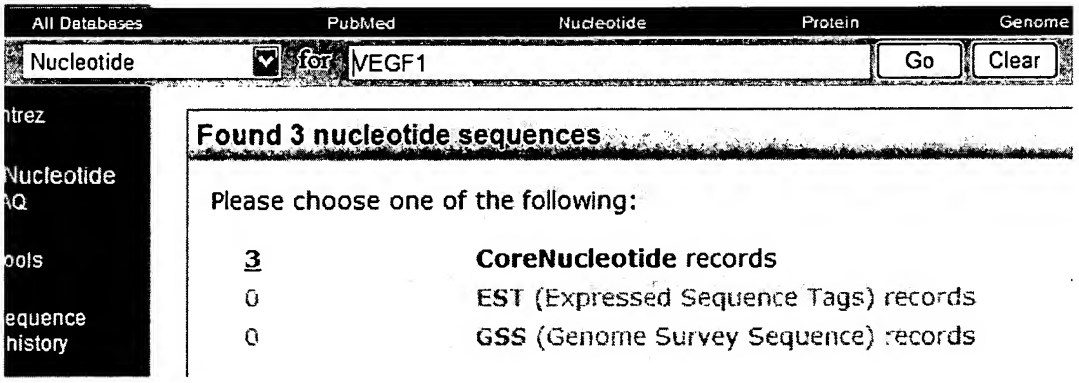
In view of the above, it is concluded that the instantly claimed invention failed to comply with the enablement requirement, thus necessitating undue experimentation for one of ordinary skill in the art to practice the entire scope of the claimed methods, as of the earliest filing date sought in the instant application. Therefore, this rejection is maintained.

Claim Rejections - 35 USC § 112, written description

Claims 1-7, 27-30, 38-43, 45, 48-50, and 53 remain rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement for the reasons of record as set forth in the Office action mailed on May 30, 2007 and for the reasons stated below.

Applicant's arguments filed on November 30, 2007 have been fully considered but they are not persuasive. Applicant argues that the two disclosed species of the claimed RNAi agent targeted to a CMV gene is representative of the claimed genus. Unlike other genes, viral genes have myriad transcripts because they constantly evolve different strains/variants. As evidenced by the publicly available nucleotide database offered by NCBI at the World Wide Web address ncbi.nlm.nih.gov/sites/entrez, the entry of "CMV" yields 584663 nucleotide sequences, which is in stark contrast to the yield of 3 nucleotide sequences for VEGF1. See below.





In view of the above, the two species of the claimed genus of CMV RNAi agents are not considered to represent the entire genus comprising various transcripts and that the inventor invented the genus claimed in the instant case, and therefore, this rejection is maintained.

Claim Rejections - 35 USC § 103

Claims 1-7, 27-30, 45, 47-50, and 52-53 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kondo et al. in view of Fire et al. and Tuschl et al. for the reasons of record as set forth in the Office action mailed on May 30, 2007 and for the reasons stated below.

Applicant's arguments filed on November 30, 2007 have been fully considered but they are not persuasive. Applicant argues that the claims as currently amended are not unpatentable over the cited references, especially because Kondo et al. do not teach or suggest the "important feature of the invention", namely the RNAi agent targeting the CMV transcript within a region common to at least two CMV mRNAs derived from the transcript. Contrary to applicant's argument, the nucleic acid sequence of SEQ ID NO:19 of Kondo et al. is complementary to that of SEQ ID NO:2 of the instant case, and therefore, the nucleic acid sequence of Kondo et al. inherently would target a region common to at least two CMV mRNAs. Accordingly, this rejection is maintained.

New Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 54-56 and 60-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting CMV expression in cells *in vitro*, does not reasonably provide enablement for the method of treating retinitis or the method of inhibiting CMV *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The same reasons stated in the previous Office action dated May 30, 2007 and on pages 3-5 herein apply as the basis to conclude that the specification does not comply with the enablement requirement and therefore one of ordinary skill in the art would not have been able to practice the entire scope of the claimed invention at the time of the invention without undue experimentation.

Again, the specification contains enabling disclosure only for *in vitro* reduction of CMV expression and that siRNA-mediated gene therapy was considered as nascent technology. The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. See *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004).

In view of the totality of the factors (see page 4 of the previous Office action) and the reasons stated above, the claimed invention is enabled only insofar as *in vitro* methods.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 54-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kondo et al. (citation of record) in view of Fire et al. (citation of record) and Tuschl et al. (citation of record).

The claims are drawn to a method of inhibiting a CMV *in vitro*, comprising exposing an infected cell to an RNAi agent that targets a region common to IE1 and IE2, the RNAi agnet is a dsRNA molecule wherein each strand is about 18-29 nucleotides in length and has two 3'-deoxythimidines and a 5'-phosphate group, wherein the dsRNA comprises SEQ ID NO:2 in which T is replaced by U, the dsRNA is contained within an expression vector.

Kondo et al. teach that CMV is a significant pathogen in immuno-compromised individuals and one of the best studied virus in the art (column 2, lines 43-57). They teach the DNA sequences common to IE1 and IE2 transcripts, which they refer to them as "CMV ie1/ie2" (column 3, lines 10-35). They teach a method of detecting CMV infection in a cell by PCR amplification using a reverse primer comprising SEQ ID NO:19 (column 4, lines 45-65; Figure 7). It is found that SEQ ID NO:19 of Kondo et al. is fully complementary to nucleotides 1-18 of the instantly claimed SEQ ID NO:2. They also teach expression vectors for expressing antisense RNA or ribozymes for gene inhibition applications (column 5, lines 1-47). Kondo et al. do not teach a method of inhibiting CMV expression comprising an RNAi agent.

Fire et al. teach that RNAi-mediated gene inhibition is advantageous over antisense approach because double-stranded RNA is more stable, the RNAi-mediated inhibition requires less concentration of the dsRNA for effective gene inhibition, and the RNAi-mediated inhibition occurs efficiently under physiological conditions (column 3, lines 20-45). They teach that the length of the double-stranded RNA is 25 nucleotides in length (column 8, lines 5-6). They teach that a gene derived from any pathogen in virus may be targeted for inhibition in cells *in vitro* such as HIV (column 8, lines 13-17; column 10, lines 8-18).

Tuschl et al. teach that dsRNA triggers RNAi and is process to 21-23 nucleotide RNA fragments in cells, thereby termed short interfering RNA (siRNA). See columns 1-2. They teach that siRNA of 19-25 nucletoides in length with 3'-deoxythymidine overhangs and 5'-phosphates mediate target-specific RNA interference (column 2, lines 35-67; column 3, lines 5-8; Figures 8B and 18-19). They teach that siRNAs comprise "U"s instead of "T"s. See Figures 5A and 8B. They teach that the thymidine overhang enhances nuclease resistance of siRNAs in cells and mediates more potent gene inhibition (column 22, lines 63-67; column 23, lines 1-4). They teach that the target gene may be a viral gene (column 5, lines 11-15).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the RNAi-mediated inhibition of Fire et al. to target IE1/IE2 transcripts of CMV of Kondo et al. by designing an siRNA molecule as taught by Tuschl et al.

One of ordinary skill in the art would have been motivated to so with a reasonable expectation of success because the CMV gene, especially the genomic region common to both IE1 and IE2, was a well-known target for antisense-mediated gene therapy as taught by Kondo et al. (column 4, lines 57-65; column 5, lines 1-47), and because targeting CMV or any viral

pathogen via RNAi mechanism in cells *in vitro* was an art-recognized goal as taught by both Fire et al. (column 8, lines 13-17; column 10, lines 8-18) and Tuschl et al. (column 5, lines 11-15). Since Fire et al. expressly teach that RNAi-mediated gene inhibition is more potent and efficient than antisense-mediated gene inhibition (column 3, lines 20-45), the skilled artisan would have been motivated to replace the antisense-mediated CMV gene inhibition of Kondo et al. with the RNAi-mediated inhibition of Fire et al. Since both 3'-deoxythimidines and 5'-phosphate group were known to increase stability and efficacy of siRNAs as taught by Tuschl et al., the skilled artisan would have been further motivated to incorporate such modifications into designing CMV siRNA molecules. Furthermore, the fully complementary sequence of the instantly claimed SEQ ID NO:2 was taught by Kondo et al. as an effective primer that amplifies the IE2 gene transcript. Although the primer sequence of Kondo et al. (SEQ ID NO:19) is complementary to nucleotides 1-18 of the 19-mer sequence of SEQ ID NO:2, one of ordinary skill in the art would have been motivated to modify the length of the anti-CMV siRNA molecule through routine optimization experimentation. Further, since sequences common to IE1 and IE2 transcripts were taught by Kondo et al. (column 3, lines 10-35) and since the factors to consider in designing effective siRNAs (length limitations, modifications) were taught by Tuschl et al. (columns 2-3, 22-23), the skilled artisan would have had a reasonable expectation of success in making the siRNA comprising SEQ ID NO:2 with 3' and 5' modifications within the optimal range of length. Accordingly, the instantly claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

No claim is allowed.

This application contains claims 8-26, 46, and 51, drawn to inventions nonelected with traverse in the reply filed on March 23, 2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. Angell/
Primary Examiner